Neural correlates of olfactory change detection

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Detecting changes in a stream of sensory information is vital to animals and humans. While there have been several studies of automatic change detection in various sensory modalities, olfactory change detection is largely unstudied. We investigated brain regions responsive to both passive and active detection of olfactory change using fMRI. Nine right-handed healthy, normosmic subjects (five men) were scanned in two conditions while breathing in synchrony with a metronome. In one condition, subjects mentally counted infrequent odors (Attend condition), whereas in the other condition, subjects' attention was directed elsewhere as they counted auditory tones (Ignore condition). Odors were delivered via a nasal cannula using a computer-controlled air-dilution olfactometer. Infrequently occurring olfactory stimuli evoked significant ($P < .05$, corrected) activity in the subgenual cingulate and in central posterior orbitofrontal cortex, but only in the Ignore condition, as confirmed by direct comparison of the Ignore session with the Attend session ($P < .05$, corrected). Subgenual cingulate and posterior orbital cortex may therefore play a role in detecting discrepant olfactory events while attention is otherwise engaged in another sensory modality.
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Introduction

Involuntary detection of change in a stream of sensory information is vital to animals and humans; for example, failing to perceive a gas leak or fire, or the odor of a predator or potential mate, could have critical consequences. While there have been several studies of automatic change detection in various sensory modalities, such as audition, touch, and vision (e.g., Downar et al., 2000), detection of olfactory change is largely unstudied. Change detection has been studied widely in the auditory modality using event-related potentials (ERPs). A negative deflection, dubbed the mismatch negativity (MMN), is observed 100–200 ms following an irregularity (i.e., deviant) in an auditory train, and is largely independent of attention (Näätänen, 1992). An analogous response in the visual modality has not been established clearly, and some argue for its absence (e.g., Alho et al., 1992; Kropotov et al., 1995); however, an MMN-like negative potential was observed in response to a change in tactile stimuli (Kekoni et al., 1997).

The sense of smell has long been regarded as a system that "constantly and automatically monitors the environment for odors" (Engen, 1991). This view suggests the possibility that pre-attentive processing (Lorig et al., 1990) and an MMN-analogue response exist in the olfactory modality (see also Pause and Krauel, 2000). Krauel et al. (1999) recorded EEG while presenting subjects with a repetitive odor train ($P = .8$) that was infrequently interspersed with a rare deviant odor ($P = .2$). Subjects were instructed to ignore the odors and focus on an auditory task (i.e., counting the word "you" in a recording cycle). A negative deflection was elicited following deviant odors (compared with repetitive odors) supporting the presence of an olfactory MMN.

Recently, neural correlates of change detection have been studied using imaging (PET, fMRI) techniques (e.g., Celsis et al., 1999; Downar et al., 2000; Liebenthal et al., 2003; Müller et al., 2002; Opitz et al., 1999, 2002; Sabri et al., 2003), although not yet in the olfactory domain. Downar et al. (2000) studied the cortical network underlying inattentive *multimodal* (auditory, visual, and tactile) and *unimodal* change detection using fMRI. Multimodal detection of change activated the bilateral temporal–parietal junction (TPJ), inferior frontal gyrus (IFG; right greater than left), right insula, left cingulate, and supplemental motor areas, whereas unimodal change activated areas associated specifically with that modality (e.g., auditory areas in temporal cortex for the auditory modality).

To uncover the previously unstudied cortical regions that mediate olfactory change detection, the current study employed fMRI and the common oddball paradigm, which periodically replaces a repeating stimulus (the standard) with an infrequent deviant. We compared two conditions: In one, subjects ignored odors while concentrating on a simple auditory counting task, as in the Krauel et al. (1999) study. In the other, subjects focused explicitly on each odor by counting the number of deviants presented. We expected a dissociation between cortical areas that respond automatically (i.e., without directed

attention) to olfactory change, and other regions involved specifically when attention is focused on detection of olfactory changes.

Materials and methods

Subjects

Nine healthy, right-handed, normosmic subjects (five men, mean age = 25.1, SD = 2.9, education = 17.0, SD = 2.3) participated in this study. Institutional Review Board-approved written informed consent was obtained from each subject. All subjects were screened by self-report for neurological and psychiatric disorders, use of psychiatric/neurological medications, and for any condition that might interfere with olfaction (e.g., acute allergic rhinitis, etc). Olfactory capacity was assessed using a 20-item version (Doty et al., 1989) of the University of Pennsylvania Smell Identification Test (UPSIT$_{20}$; mean = 17.8, SD = 1.1).

Odor stimulation

Odors were delivered via an 8-channel, computer-controlled, air-dilution olfactometer with airflow generated by an oil-less pump, filtered through a charcoal filter, and humidified. Solenoid valves injected air from one of three channels (two odor and one odorless control) into a continuous air stream (1 L/min) for a constant 2 L/min total system flow. Each odorant vessel contained a polypropylene disk saturated with odorant solution or 1,2-propanediol (propylene glycol; control). The two-odorant solutions used were 1% by volume grass oil in 1,2-propanediol and 100% leather oil (International Flavors and Fragrances). Air was delivered to the subject with a small, birhinal Teflon® nasal cannula. Switching between control air and odorants evoked no change in flow or somatosensory cue. A Pentium-III laptop running Windows98 and DASYLab (IOtech, Inc., Cleveland, OH) controlled the system. A Personal DAQ/56 module (IOtech, Inc., Cleveland, OH) controlled the solenoid valves.

Breathing technique and auditory stimulation

Subjects were instructed to breathe nasally in time with a metronome delivering alternating high and low pitch tones every 2.5 s. Tones were 100 ms in duration and ~95 dB/SPL in intensity. Subjects inhaled on each low pitch tone (1.2 kHz) and exhaled on each high pitch tone (1.0 kHz) for a respiration rate of 12 min^{-1}, the average human respiration rate (Chesnutt and Prendergast, 2004). Auditory stimuli were delivered binaurally via plastic sound conduction tubes threaded in foam earplugs, inside non-ferrous air-conducting headphones. Tone presentation was controlled by a personal computer running E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) and a pneumatic-based audio system (Avotec, Jensen Beach, FL). Odors were presented during the subjects' inhalation, whereas control flow without odorants was used during the exhalation periods.

Procedure

A boxcar block design was employed under two conditions, each condition performed twice. For both conditions, five 50 s standard (S) blocks consisting of 10 grass odor presentations alternated with four 50 s S + deviant (D) blocks of 8 grass and 2
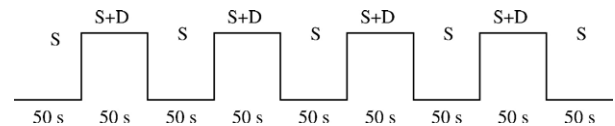

Fig. 1. Schematic diagram of the experiment. Five 50 s standard blocks (S) consisting of 10 grass odor presentations alternated with four 50 s standard + deviant blocks (S + D) of 8 grass and 2 leather odor presentations for a total of 9 blocks/scan. SOA = 5 s.

leather odor presentations for a total of 9 blocks/scan (see Fig. 1). The two odors were not counterbalanced as standard and deviant stimuli. The position of the deviants in the S + D blocks was pseudorandom for each condition and repetition, but consistent between subjects. The deviants were placed such that they never occurred on the first or last two odors of S + D blocks, and so that the two deviants had at least two standards separating them. In the Attend condition, subjects were instructed to attend actively to the quality of the odors presented, and mentally count the number of deviants that occurred throughout the scan. In the Ignore condition, subjects were instructed to ignore the odors and mentally count the low pitch tones. The two conditions were counterbalanced across subjects. Subjects were asked to report their total count (of deviants or tones) following each scan condition to assure compliance and adequate task performance.

Image acquisition

Functional images were acquired using a dual-echo spiral-in (DSPIN) BOLD pulse sequence on a 1.5 T GE Signa LX Horizon scanner (General Electric, Waukesha, WI). Each imaging session produced 224 images for analysis, excluding images discarded to account for presaturation (Bandettini et al., 1993). Twenty-two 3.8 mm thick axial slices with no interslice gap were used to acquire the functional data (Repetition Time/First Echo Time/Second Echo Time (TR/TE$_1$/TE$_2$) = 2000/35/70 ms, Flip Angle (FA) = 90°, Field-of-View (FOV) = 24 × 24 cm, matrix 64 × 64). High-resolution, heavily T1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices, 3D Spoiled-Grass sequence (SPGR), slice thickness = 1.2 mm, TR/TE = 35/8 ms, FA = 30°, FOV = 24 × 24 cm, matrix 256 × 128). Subjects were fitted to a bite-bar, made with dental impression material, which was attached to the head coil to minimize head motion.

Image processing and data analysis

SPM99 (Wellcome Department of Cognitive Neurology, University College, London, UK), fixed effect model, was used for data analysis; statistical inferences are thus valid only for the sample reported here. DSPIN images were corrected for intra-subject motion using affine, rigid-body transformations. High-resolution 3D SPGR anatomic images of each subject were used to derive the parameters used for non-linear warping (7 × 8 × 7 basis functions, 12 iterations) of the subjects' images into stereotactic (Montreal Neurological Institute; MNI) space. These parameters then were used to transform the DSPIN images into the same coordinate space with an isotropic voxel size of 2 mm. Images were smoothed using an 8 mm (FWHM) isotropic Gaussian kernel. A boxcar function, convolved with SPM's standard hemodynamic reference function, was used to model the data for each subject/scan. High-pass (cutoff period = 204 s) and low-pass (4 s FWHM Gaussian smoothing filter) filters were used to correct for low and high frequency artifacts, respectively. *t* contrasts consisted of
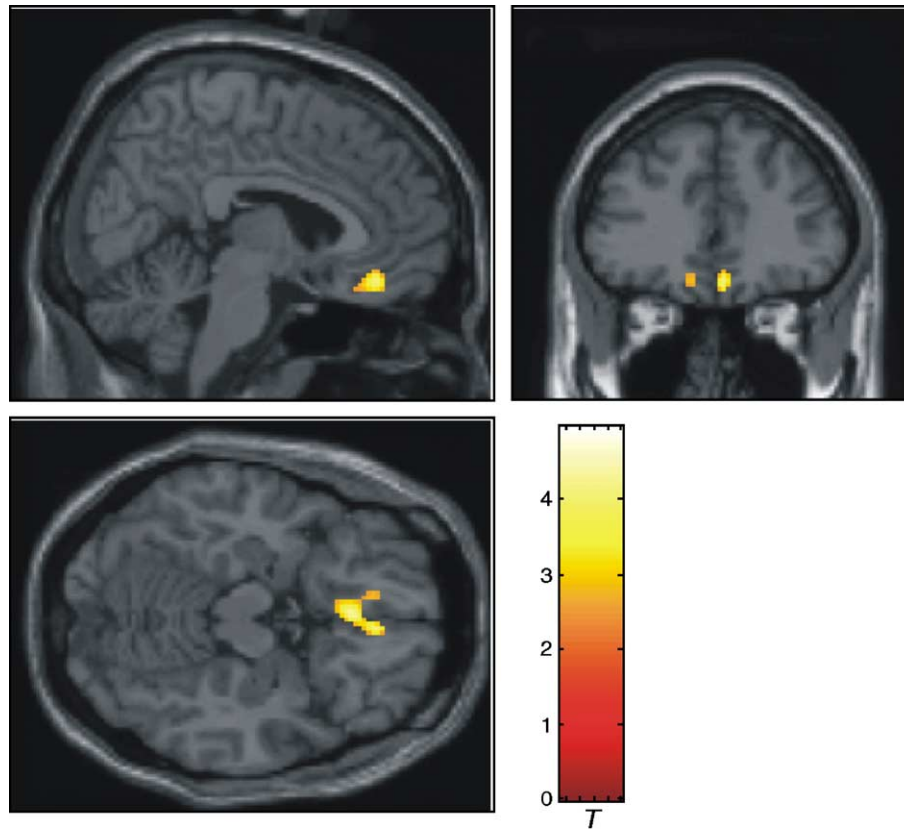
Fig. 2. Ignore condition: S + D compared with S produced greater activation in the posterior and central orbitofrontal cortex and the subgenual cingulate. Display threshold, $P < .005$, uncorrected. R = R.

Attend (S + D) > S (i.e., attend the odors), Ignore (S + D) > S, and Ignore [(S + D) − S] > Attend [(S + D) − S]. A corrected voxel statistic threshold of $P < .05$ was used to establish statistical significance. The coordinates reported are in MNI space.

Results

Behavioral performance

Subjects performed the task satisfactorily. In the Attend condition, the mean number of deviant odor counts was 9.5 (SD = 2.3), while in the Ignore condition, the mean number of low pitch tone counts was 93 (SD = 3.8).

Imaging results

In the Ignore condition, the (S + D) > S contrast revealed activation in posterior and central orbitofrontal cortex (OFC; 6, 38, −16; $t = 4.18$) extending to the subgenual cingulate (−6, 26, −10; $t = 4.96$) (Fig. 2). Activation was largely absent in the Attend condition ($P > .05$; whole brain correction) (Fig. 3). However, examination of the orbitofrontal area (olfactory association cortex) with an identified prior volume (a large 112 × 40 × 40 mm rectangle covering most of orbital cortex, and centered at 0, 40, −10; see Kareken et al., 2004) revealed a small cluster of activation (41 voxels) in right orbitofrontal cortex (26, 50, −8; $t = 3.27$, $P < .003$ corrected).

Consistent with the within-condition effects, the interaction between attentional set (Attend vs. Ignore) and stimulus block

(S vs. S + D), as depicted in the contrast Ignore [(S + D) − S] > Attend [(S + D) − S], revealed activations with local maxima in the OFC (6, 40, −16; $t = 4.97$; 2, 32, −18; $t = 5.35$) and cingulate (−2, 26, −12; $t = 6.20$). Although not in any known olfactory area, we also noted a smaller cluster of activity in the anterior/ventral temporal area, bilaterally (−40, 14, −38; $t = 5.71$; 34, 10, −44; $t = 5.11$). Attend [(S + D) − S] > Ignore [(S + D) − S] revealed activation in the right OFC (24, 48, −8; $t = 4.22$).

Discussion

This study investigated the cortical network underlying detection of odor change and its modulation by attention. During the Ignore condition, subjects were required to disregard deviant olfactory events by concentrating on a primary auditory task.[1] In

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[1] In MMN studies, the difficulty of the primary task that subjects perform during Ignore conditions varies between easy tasks, such as reading, watching a film, or no specific task at all, and more demanding tasks, such as visual search and n-back. In this and other studies, we cannot rule out the possibility that subjects did not entirely ignore the olfactory stimuli in the Ignore condition. This is a common problem in MMN research, and indeed the term "ignore" might be misleading, although its use is standard in this field. However, given subjects' relatively good performance on the auditory task in the Ignore condition, their attention was at least diverted away from the odors more than during the Attend condition.
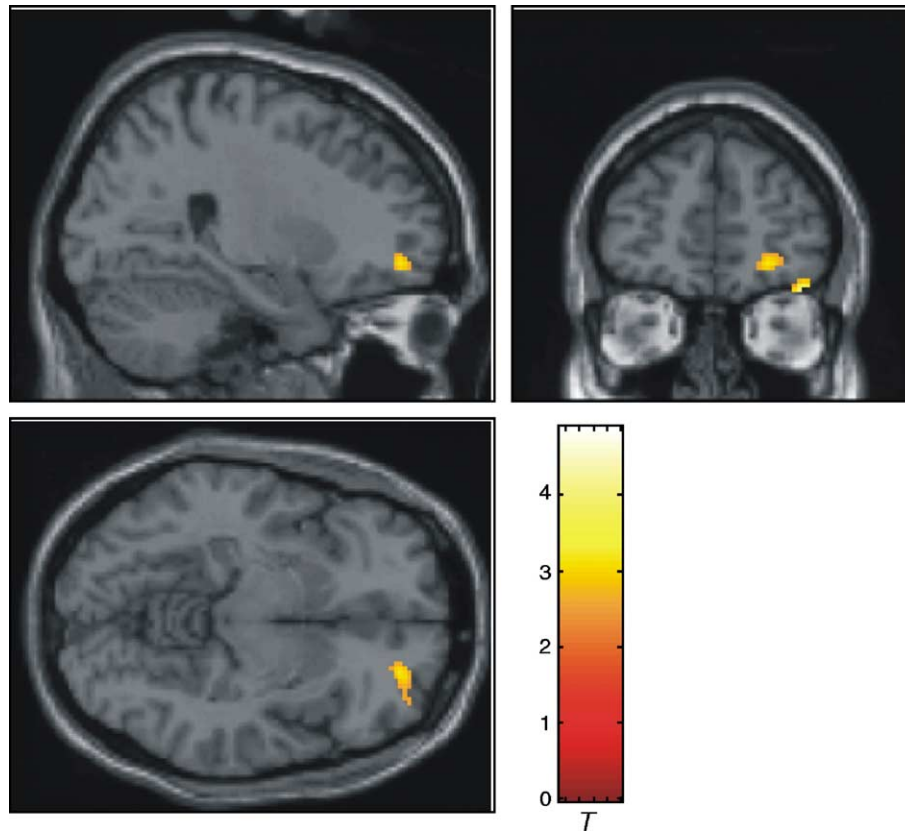
Fig. 3. Attend condition: S + D compared with S produced a small amount of greater activation in right orbitofrontal cortex. Display threshold, *P* < .005, uncorrected. R = R.

the Attend condition, subjects concentrated on the odors while ignoring the auditory events. When olfactory stimuli were ignored, the shift from standard to rare deviant odors activated the central OFC and the subgenual cingulate. With attention directed explicitly to olfactory stimulation, there was only a small activation in the right OFC.

Olfactory processing begins in the bipolar receptors of the olfactory mucosa. These cells send efferent projections to the olfactory bulbs' mitral and tufted cells. These, in turn, project to the olfactory tract, synapsing on neurons in the anterior olfactory nucleus, olfactory tubercle, piriform cortex, amygdaloid complex, and entorhinal cortex (Price, 1990). Piriform cortex, the largest cortical recipient of lateral olfactory tract fibers, sends direct projections to caudal orbital areas, which also receive indirect input from dorsomedial complex of the thalamus (Mesulam and Mufson, 1985). Zatorre et al.'s (1992) early PET study of olfactory sensory stimulation in humans revealed increased regional cerebral blood flow to bilateral medial temporal piriform and right orbitofrontal areas, consistent with the known anatomy and with other subsequent brain imaging studies (see Zald and Pardo, 2000, for a review).

We did not observe piriform and surrounding medial temporal activation in the current study. The probable reasons are that odorants were present throughout imaging, without an "off" period against which to contrast odorant stimulation. By contrast, and despite the constant olfactory stimulation, we did observe variation in orbitofrontal signal as a function of both stimulus frequency (rare vs. frequent stimulation) and the

interaction between stimulus block (S vs. S + D) and attentional set (Attend vs. Ignore). The most robust OFC activation from the S + D blocks occurred when the odors were ignored. Because the S and S + D blocks were identical in auditory stimulation, this activation is likely to be unrelated to auditory processing. Furthermore, it is unlikely that the OFC activation is merely a consequence of greater neural responses to the infrequently presented deviant odors brought about by habituation to the frequently presented standard odors. Despite the fact that identical stimuli were used in each condition, a specific activation from the deviant odor was present only when attention was directed away from the odors as observed in the interaction Ignore [(S + D) − S] > Attend [(S + D) − S]. If this effect was due to odor frequency, then similar activation would have been observed in the contrast Attend [(S + D) > S] > Ignore [(S + D) > S]. In addition, these interactions controlled for signal differences that could potentially be attributed to any properties that are specific to the odorant itself. Taken together, these results suggest that the posterior/medial OFC may play a role in inattentive perception of odor change.

Similarly, cingulate cortex (CC) was activated only when the odors were ignored, as observed in the contrasts Ignore (S + D) − S and Ignore [(S + D) − S] > Attend [(S + D) − S]. The CC has been implicated in selection and conflict tasks, such as the Stroop task (Leung et al., 2000; Posner and Peterson, 1990), as well as in passive deviant detection in auditory or visual oddball paradigms (Baudena et al., 1995). The Ignore condition of the current study required subjects to focus on the

auditory stimulation (counting tones) while breathing odorants. The combination of a bimodal selective attention task and deviance occurrence in the unattended modality may well have contributed to the cingulate activation.

A small right and lateral OFC region was activated when subjects attended to and detected the deviant odors. Because subjects attended to the odors during both S and S + D blocks, this activation cannot be attributed to general olfactory attention, but rather to target detection. Greater OFC activation is observed in the course of judgments about odor quality (Anderson et al., 2003; Gottfried and Dolan, 2003; Savic et al., 2000). In addition, subjects with either left or right frontal lobectomies have difficulty identifying and discriminating between odors, with right orbital lesions producing the severest deficit (Jones-Gotman and Zatorre, 1988; Zatorre and Jones-Gotman, 1991).

On the other hand, animal work also clearly shows that orbital areas respond to stimulus anticipation, such as with approach behavior in advance of odor sampling and just prior to odor sampling (Lipton et al., 1999), with initiation of odor recognition memory trials (Ramus and Eichenbaum, 2000), and with signals of odor availability and the intent to sample (Alvarez and Eichenbaum, 2002). Nobre et al.'s (1999) human imaging study revealed bilateral orbito- and lateral frontal areas that responded to violated visual expectation. Thus, it is possible that the OFC activation in the Attend condition was related to either monitoring of expected deviation (that is, subjects were told to focus on and count the oddball odors), or to the violation in the repetitive train itself.

In summary, these data suggest the possibility that the posterior orbital/subgenual cingulate may play an important role in inattentive odorant detection. Right frontal activity during directed attention may have stemmed from analysis of quality differences or from anticipation of forthcoming deviant events. Future research is needed to address these possibilities.

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